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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Ronald S. VLADYKA, Jr., et al.**

Serial No.: **09/708,581**

Group Art Unit: **1623**

Filed: **November 9, 2000**

Examiner: **Everett White**

Entitled: **MICROCRYSTALLINE CELLULOSE CUSHIONING GRANULES**

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I hereby certify that this paper is being sent via First Class Mail to the Assistant Commissioner for Patents on the date shown below.

On April 25, 2003

By Luis C. Rousseau

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.191

This is an appeal from the rejections set forth in the Final Rejection dated October 3, 2002 (hereinafter "the Final Rejection"). Appellant respectfully submits that the rejections in the Final Rejection were made in error, and that these rejections should be reversed for the reasons set forth below.

I. The Real Party in Interest

The real party in interest in the present appeal is R.P. Scherer Technologies, Inc., 2030 East Flamingo Road, Suite 260, Paradise Valley, Nevada 89119, to whom an undivided interest in the above-captioned application has been assigned by virtue of an assignment by the inventors to

the FMC Corporation recorded on January 23, 2001 at reel 011469, frame 0055, and a subsequent assignment from the FMC Corporation to R.P. Scherer Technologies, Inc, recorded on May 7, 2002 at reel 012884, frame 0216.

II. Related Appeals and Interferences

The Appellant is unaware of any pending appeals or interferences related to the present appeal.

III. The Status of the Claims

Claims 1 through 26 are currently pending in the present application and stand rejected in a Final Rejection dated October 3, 2002. The rejection of claims 1 through 26 is hereby appealed. A copy of the currently pending claims 1 through 26 is attached as an appendix hereto.

IV. The Status of any Amendments Filed after Final Rejection

A single amendment after the Final Rejection was filed on April 25, 2003 to correct a typographical error in Comparative Examples B-C of the specification. The Examiner has not yet responded to this amendment at the time of filing this Appeal Brief.

The Advisory Action dated January 24, 2003, indicates that proposed amendments submitted after the Final Rejection have been entered for the purpose of appeal. However, this appears to be an error since the applicant did not propose any amendments to the application after issuance of the Final Rejection dated October 3, 2002.

V. Summary of the Invention

The microcrystalline cellulose granules of the present invention may be employed as a component in a tablet, for example, for the controlled release of a vitamin or pharmaceutical composition. The microcrystalline cellulose granules of the invention may be used in such tablets as cushioning granules, for the purpose of protecting the controlled release particles of the tablet during the application of high pressure in the process of forming of the tablet. It has been found that microcrystalline cellulose granules made in accordance with the process of the present invention and having the properties of the product of claims 16-24 of the present application, help to protect controlled release particles from damage or destruction during the application of high pressure, for example, in a tabletting process, thereby substantially maintaining the controlled release properties of such controlled release particles when the particles are incorporated in a tablet by application of high pressure. This permits the formulation of certain controlled release vitamins and pharmaceuticals in a solid unitary tablet. This is in contrast to the administration of these products in a hard gelatin capsule containing a plurality of the controlled release particles.

In a first aspect, as claimed in independent claim 1, the present invention relates to a method for preparing porous microcrystalline cellulose granules. The method comprises granulating microcrystalline cellulose with a granulating fluid to provide a granulated microcrystalline cellulose. The granulating fluid comprises water and a water-miscible, volatile, polar organic solvent. The method further comprises drying the granulated microcrystalline cellulose at a controlled rate for a time sufficient to remove at least substantially all of the polar organic solvent from the granulated microcrystalline cellulose without removing at least a

substantial portion of the water from the granulated microcrystalline cellulose. The granulated microcrystalline cellulose is not extruded or spheronized in this controlled-rate drying step. Subsequent to the controlled-rate drying step, at least a substantial portion of the water is removed from the granulated microcrystalline cellulose. Additional features of this aspect of the invention are claimed in claims 2 through 15.

The controlled-rate drying step of the process of the present invention is important because it results in less water from the granulating fluid being hydrogen bonded to the microcrystalline cellulose, as compared to the use of a drying process, which does not remove the organic component of the granulating fluid at a controlled rate. See e.g. specification at page 6, lines 14-19. Hydrogen bonding between the water component and the microcrystalline cellulose generally leads to denser, less porous granules which may not provide as much cushioning when employed in a tablet, as comparable granules dried using the controlled drying step of the present invention. See page 6, lines 14-19 of the specification.

In a second aspect, as claimed in independent claim 16, the present invention relates to porous, microcrystalline cellulose granules having an irregular shape. The granules have a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc and a mean particle size of from about 250 microns to about 1500 microns. Additional features of this aspect of the invention are claimed in claims 17 through 24.

VI. Issues on Appeal

Appellant believes that the various issues to be considered on appeal may be concisely summarized as follows:

Issue 1: Whether claims 1 to 13 are unpatentable under 35 U.S.C. § 103(a), as obvious over U.S. Patent No. 6,123,964, issued to Asgharnejad et al (hereinafter "Asgharnejad") in view of U.S. Patent No. 5,725,886, issued to Erkoboni et al. (hereinafter "Erkoboni").

Issue 2: Whether claims 14-16, and 18-26 are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,149,943, issued to McTeigue et al. (hereinafter "McTeigue").

Issue 3: Whether claim 17 is unpatentable under 35 U.S.C. § 103(a) as obvious over McTeigue in view of U.S. Patent No. 6,117,451, issued to Kumar (hereinafter "Kumar").

VII. Grouping of Claims

Group I – Claims 1-2, 4-8, and 10-13.

Group II – Claim 3.

Group III – Claim 9.

Group IV – Claims 14-16, 18 and 20-26

Group V - Claim 19

Group VI – Claim 17

VIII. Argument

The three issues under appeal relate to the propriety of rejections under 35 U.S.C. § 103(a) for alleged obviousness of the claimed subject matter. Appellant respectfully submits, however, that none of the rejections under appeal has set forth a *prima facie* case of obviousness. It is well-established that:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *quoted in* M.P.E.P. § 2143.

It is similarly well-established that, "if the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence" of non-obviousness. *See* M.P.E.P. § 2142.

Appellant respectfully submits that the Examiner has not established a *prima facie* case of obviousness since with respect to each issue, the Examiner has not established one or more of the following: (1) that the cited prior art teaches or suggests all of the limitations of the pending claims, (2) that there is a reasonable expectation of success found in the prior art, and (3) that there is some suggestion or motivation to modify or combine the references in the manner

required to arrive at the presently claimed invention, which is found in the prior art. Accordingly, Appellant respectfully requests that the rejections in the Final Rejection be reversed.

Issue 1: Whether Claims 1 to 13 are obvious over Asgharnejad in view of Erkoboni.

A. The Rejection

Claims 1-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Asgharnejad in view of Erkoboni. The rationale for this rejection was originally set forth in the Office Action dated May 6, 2002, as follows:

> "The Asgharnejad et al patent discloses a process comprising the steps that involves [sic] (1) forming a powder blend of the active ingredient with a binder/diluent, a first diluent, a second diluent and a disintegrant, using a mixer; (2) wet granulating the powder blend by adding a solution of ethanol/water to the powder blend; (3) drying the granules to remove the ethanol/water with heated air in a fluid bed dryer or tray dryer (see column 2, line 63 to column 3, line 6). See column 3, lines 21-29 of the Asgharnejad et al patent wherein the binder/diluent is pregelatinized starch; the first diluent is microcrystalline cellulose; and wherein it is indicated that the solution of ethanol/water is in a range of 0% to 80% ethanol in water (w/w). The ethanol/water solution used in the Asgharnejad et al patent meets the polar organic solvent requirement disclosed in the claims..."

See page 4, lines 6-16 of the May 6, 2002 Office Action.

B. Group I – Claims 1-2, 4-8, and 10-13

1. The Rejection of Claims 1-2, 4-8 and 10-13 Under 35 U.S.C. §103(a)

From the fact that the Examiner rejects claim 1 under 35 U.S.C. §103(a) rather than under 35 U.S.C. §102(b), it can be concluded that the Examiner considers that claim 1 is novel over Asgharnejad since otherwise the Examiner should have rejected claim 1 over Asgharnejad under 35 U.S.C. §102(b). However, the applicant can find no indication in the record of what feature(s)

of the subject matter of claim 1 of the present application the Examiner considers to be lacking from the Asgharnejad patent.

The Examiner does not rely on the Erkoboni reference in his rationale for rejecting claim 1 in the Office Action dated May 6, 2002. This is supported by the record. More specifically, in the August 6, 2002, response to the May 6, 2002 Office Action, the applicant noted that, "The Examiner relies on Erkoboni et al. as disclosing compositions containing a combination of microcrystalline cellulose and hydrocolloids presumably in relation to claim 7 of the present application." See page 6, lines 1-3 of the August 6, 2002, Amendment. In the immediately subsequent Final Rejection the Examiner confirmed that this characterization of the Examiner's position relative to the Erkoboni reference was correct when he stated, "Applicants [sic] assessment of the Erkoboni et al. patent in the rejection of the claims is correct." See page 3, lines 1-2 of the Final Rejection. Also, there does not appear to be any mention in the record of any specific facts or evidence showing that the Examiner relies on Erkoboni in support of his rejection of claim 1. Thus it appears from the record that the Examiner only relies on Erkoboni in support of his rejection of claim 7, and that Erkoboni is not employed in the rejection of claim 1.

2. Claim 1 is Novel over Asgharnejad

The applicant believes that claim 1 is novel over Asgharnejad. Specifically, there is no teaching or suggestion in Asgharnejad to carry out the drying of the granulated microcrystalline cellulose at a controlled rate for a time sufficient to remove at least substantially all of the polar organic solvent.

It is well settled that, "the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification." In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) and MPEP §2111.01. In the present case, the term, "controlled rate" has been given a special meaning by the applicant in the specification at page 6, lines 4-6 of the specification which states, in relevant part, that "[T]the rate of the controlled drying step is controlled by carrying out the drying with no more than a minimal input of heat..." This statement clearly defines the meaning of the term, "controlled rate" as that term is used in the claims of the present application and thus this definition of the term, "controlled rate" should be applied by the Examiner when giving claim 1 its broadest reasonable interpretation for the purpose of examination. In re Zletz, 893 F.2d at 321. This interpretation of "controlled rate" is consistent with the examples of the process of the invention contained in the present application, since, in each of the examples, the drying process contains a step carried out at ambient temperature without the input of heat.

The teaching of Asgharnejad relied on by the Examiner is to dry the granules by removing the ethanol/water with heated air in a fluid bed dryer or tray dryer for 10 minutes to 24 hours. See Asgharnejad at col. 3, lines 4-6. From this teaching, two important points about the Asgharnejad drying process can be learned. First, Asgharnejad always uses heated air for its drying step. Second, Asgharnejad only cares about removing the ethanol/water granulating fluid, and contains no teaching that it is important or desirable to remove the ethanol component of the granulating fluid at a controlled rate, or that a beneficial result could be obtained by removing the ethanol component at a controlled rate. Moreover, despite the fact that Asgharnejad contains a detailed

description of the various components that may be included in its tablets, Asgharnejad does not contemplate the use of controlled release particles. Thus, since the formulations of Asgharnejad do not contain controlled release particles, Asgharnejad is not concerned with the goal of the present invention of providing microcrystalline cellulose granules that can provide a cushioning effect to such controlled release particles during a tabletting process.

Further, Asgharnejad exemplifies only a single drying step and this same drying step is employed in Examples 19, 20, 23 and 25 of Asgharnejad. See col. 39, lines 28-30; col. 40, lines 41-43; col. 41, lines 44-46 and col. 42, lines 49-51 of Asgharnejad. The exemplified drying step of Asgharnejad dries the wet granules at 47°C in a tray dryer or a fluid bed dryer for approximately 3.0 hours. This is not the same as the "controlled rate" drying step of claim 1 of the present application.

3. No *Prima Facie* Case of Obviousness has been Made by the Examiner

Thus, returning to the elements required for a case of *prima facie* obviousness, it is clear that the Examiner's position that claim 1 is obvious over Asgharnejad falls short of making out a *prima facie* case of obviousness for at least the following reasons.

First, Asgharnejad does not teach or suggest conducting the drying of the granulated microcrystalline cellulose at a controlled rate for a time sufficient to remove at least substantially all of the polar organic solvent. As demonstrated above, drying at a controlled rate has been defined by the applicant as carrying out the initial drying step with no more than a minimal input of heat to remove the organic solvent. The general teaching of Asgharnejad requires drying in

heated air and the exemplified drying process of Asgharnejad is carried out at 47°C for 3 hours. The use of heated air to provide a drying environment of 47°C, i.e. about 27°C above ambient temperature, for a period of 3 hours, as in Asgharnejad, involves more than a minimal input of heat as would be required to meet the "controlled rate" limitation of claim 1 of the present application. Thus, Asgharnejad nowhere suggests to the skilled person to dry with a minimal input of heat, as is required to meet the "controlled rate" limitation of claim 1 of the present application and thus, this element of claim 1 is clearly lacking from the teachings of Asgharnejad.

Rather, the skilled person reading Asgharnejad would be motivated to use a significant input of heat in the drying step by the general teaching of Asgharnejad found in col. 3, lines 4-6 that heated air should be used in the drying step. Also, from a review of the Examples of Asgharnejad, the skilled person would conclude that more than a minimal amount of heat input would have to be employed in the drying step since Asgharnejad exemplifies drying at a temperature 27°C above ambient temperature, and maintaining that significantly elevated temperature for three hours. This will require input of heat to first raise the temperature to 27°C above ambient temperature, and then a further continuing input of heat to maintain the temperature at that level for three hours.

The Examiner has taken the position that the present claims do not distinguish over Asgharnejad "...since the instant claims do not set forth a critical temperature and critical time for carrying out the drying process that is substantially different from the temperature and time that is disclosed in the Asgharnejad et al. patent." See Final Rejection, page 2, lines 16-18. This is not correct, as discussed above, since the term, "controlled rate" in the present claims requires drying

with a minimal input of heat. The temperature and time disclosed in Asgharnejad of 47°C for 3.0 hours is significantly different than that claimed in claim 1, since more than a minimal amount of heat must be input in the drying process of Asgharnejad to raise the drying temperature 27°C above ambient temperature and to maintain the drying temperature at that elevated temperature for a period of three hours.

The Examiner also took the position that,

> It is also well known in the art that ethanol will evaporate before water in a drying process to remove a solvent comprising ethanol and water. The ethanol and water mixture in the Asgharnejad et al patent embraces the polar organic solvent and water mixture in the instant claims wherein Claim 1 discloses the removal of substantially all of the polar organic solvent before removing a substantial portion of the water. Hence, the instantly claimed two step drying process appears to be only a masquerade of what will normally occur for the evaporation of a solvent mixture comprising water and a polar organic solvent, ...

See the Final Rejection at page 2, lines 21-29. The applicant does not disagree that, if the ethanol/water present in the granulate behaves as a single-phase solvent mixture of ethanol and water, ethanol will evaporate before water in a drying process to remove a solvent comprising ethanol and water.

However, there are two problems with this position taken by the Examiner. First, merely evaporating the ethanol before the water is not the invention as claimed in claim 1. Rather, the applicant has found that it is important when evaporating the ethanol during the drying process, that this step be carried out at a <u>controlled rate</u> since otherwise the resultant granules will be too dense to provide the desired cushioning properties for cushioning controlled release particles during a tabletting step. See e.g. specification at page 6, lines 14-19. Thus, in order to meet this limitation of claim 1, it is not enough to

demonstrate that the ethanol of Asgharnejad is removed before the water, as the Examiner suggests. Rather, the Examiner must also demonstrate that the ethanol is removed at a controlled rate, i.e. with a minimal input of heat in the drying step. Asgharnejad does not teach or suggest this specific aspect of the present invention.

In addition, the present specification contains Comparative Examples B-C which employ a one-step drying process which does not use the controlled rate drying step of claim 1. Instead, the granules of Comparative Examples B-C were tray dried overnight at 50°C. This drying temperature is very close to the 47°C drying temperature of the drying step employed in the examples of Asgharnejad. Moreover, drying overnight, (i.e. up to 16 hours) falls clearly within the 10 minutes to 24 hour drying period disclosed by Asgharnejad at col. 3, lines 4-6. Upon tabletting of the compositions dried by the methods of Comparative Examples B-C, it was found that, "Both sets of tablets [sic – granules] were found to be too dense to provide adequate cushioning properties."[1] Thus, Comparative Examples B-C confirm the conclusion at page 6, lines 15-19 of the specification that use of a single step drying process without a controlled rate drying step such as is disclosed by Asgharnejad produces a different, denser granule that exhibits poor cushioning properties.

[1] Comparative Examples B-C erroneously refer to the "tablets" as being too dense to provide adequate cushioning properties. From a reading of the specification, it is clear that it is the granules that provide cushioning properties when incorporated in tablets. See e.g. page 6, lines 15-19 of the specification. Thus, the skilled person would understand that Comparative Examples B-C teach that the granules, not the tablets, were too dense to provide adequate cushioning properties. On April 25, 2003, the Appellant filed an Amendment After Final Rejection for the purpose of correcting this minor typographical error in Comparative Examples B-C.

Accordingly, the evidence of record, especially Comparative Examples B-C, contradicts the conclusion of the Examiner that the instantly claimed two-step drying process appears to be only a masquerade of what will normally occur in the Asgharnejad drying step. Moreover, the Examiner has presented absolutely no evidence in support of his position.

The second problem with the Examiner's position is that the analysis is based on the underlying conclusion that the granulating fluid contained in the granulate will behave as a solvent mixture during the drying step.[2] However, the Examiner has not offered any evidence in support of this underlying conclusion. In fact, whether the granulating fluid behaves as a solvent mixture during the granulating step, may depend on a number of factors such as the amount of granulating fluid used in the granulating step, relative to the amount of solid material in the granulated mixture, whether and how much ethanol and/or water is adsorbed on the microcrystalline cellulose, the degree of hydrogen bonding between the ethanol and the microcrystalline cellulose, the degree of hydrogen bonding between the water and the microcrystalline cellulose, as well as the conditions to which the granulated mixture is subjected. For example, the specification indicates that there will most likely be hydrogen bonding of the granulating fluid to the microcrystalline cellulose. See e.g. page 6, lines 15-19 of the specification. Also, the skilled person will

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[2] The Applicant, in response to the Final Rejection, argued that an ethanol/water solvent mixture forms an azeotrope. However, upon further analysis of this argument during the drafting of this appeal brief, it appears that this argument is incorrect since the evidence tends to indicate that the ethanol/water granulating fluid will not behave as a solvent mixture, as discussed below, and because it appears that a solvent mixture having the composition of an ethanol/water azeotrope (i.e. about 95% ethanol) will not be formed in the process of the invention. Thus, applicant's previous argument referencing azeotropes is hereby withdrawn.

expect from a common general knowledge of chemistry that polar molecules, such as ethanol and water, would tend to hydrogen bond with and/or adsorb onto the surface of cellulosic materials, in which case the ethanol/water granulating fluid will not behave as a solvent mixture during the drying step. Thus, the Examiner's underlying conclusion that the ethanol/water granulating fluid of Asgharnejad will behave as a solvent mixture during the Asgharnejad drying step is highly questionable since it is completely unsupported by evidence and because statements made in the specification, as well as the common general knowledge of a skilled person, tend to contradict this underlying conclusion. Therefore, the Examiner's position that the drying step of Asgharnejad is the same as that of claim 1 should be disregarded for this additional reason.

In the Advisory Action dated January 24, 2003, the Examiner takes the further position that, "Applicants [sic] argument is not persuasive since the claimed two step drying process results because of the use of an excess amount of water in the process." Advisory Action at page 2, lines 5-6. This statement is not understood because the Examiner has not clearly indicated what he means by "an excess of water" since the relative term, "excess" has not been related to a reference point. If the Examiner means, an excess of water, relative to the amount of ethanol, then this statement is clearly incorrect since the specification discloses that granulating fluids containing up to 85% ethanol and 15% water can be employed in the process of the invention. See page 6, lines 26-27 of the specification. Also, Example 1 of the present application, which exemplifies a two-step drying process, employs a granulating fluid containing 1000 ml of isopropyl alcohol and about 232-248 ml of water, assuming the density of water to be about 1

gram/ml. The Examiner's statement is also not understood since he did not explain why he concludes that a two-step drying process results due to the use of an excess amount of water in the process.

Also, the Examiner takes the position that "[s]ince the amount of ethanol/water solvent used in the Asgharnejad et al patent is equivalent to the amount of ethanol/water used in the present claims, the drying step disclosed in the Asgharnejad et al patent embraces the drying step of the instantly claimed process." Advisory Action at page 2, lines 5-7. First, it is not clear what the Examiner means by "embraces." Second, it is clear from the above-discussion that the drying process of Asgharnejad is significantly different from the drying process of the present invention. Thus, this statement also does not provide sufficient factual, evidentiary or legal justification to support the Examiner's rejection.

Erkoboni also does not teach or suggest the controlled drying step of the present invention, Erkoboni provides no motivation to employ such a controlled drying step, and Erkoboni does not provide any basis for concluding that such a controlled drying step would provide any beneficial effect. More importantly, however, the teachings of Erkoboni appear to be limited to the use of water as the granulating fluid and thus there would be absolutely no reason, in the context of the Erkoboni drying process, to use a controlled rate drying step to remove polar organic solvent from the granulates of Erkoboni, since it does not appear that Erkoboni even employs polar organic solvent in the granulation step.

In addition to failing to show that Asgharnejad and Erkoboni disclose every feature of the process of claim 1 of the present application, the Examiner has also failed to make out a *prima*

facie case of obviousness because he has not demonstrated that there is some suggestion or motivation in Asgharnejad for employing a drying step carried out at a "controlled rate" to remove substantially all of the ethanol from the granules. Finally, the Examiner has also failed to make out a *prima facie* case of obviousness because has not demonstrate that Asgharnejad provides an expectation of obtaining some benefit, such as improved cushioning granules, by employing a drying step carried out at a controlled rate to remove substantially all of the ethanol from the granules. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *quoted in* M.P.E.P. § 2143.

Accordingly, for at least the foregoing reasons, the Examiner's rejection of claim 1 over a combination of Asgharnejad and Erkoboni should be reversed.

Claims 2, 4-8 and 10-12 depend, directly or indirectly, from claim 1. Because claim 1 is not obvious over Asgharnejad in view of Erkoboni for the reasons given above, it follows by statute that claims 2, 4-8 and 10-12 are also not obvious over a combination of Asgharnejad in view of Erkoboni for at least the same reasons. Accordingly, Appellant also respectfully requests that the rejection of claims 2, 4-8 and 10-12 under 35 U.S.C. § 103(a) be reversed.

C. Group II – Claim 3

Claim 3 depends indirectly, from claim 1. Because claim 1 is not obvious over Asgharnejad in view of Erkoboni for the reasons given above, it follows by statute that claim 3 is also not obvious over a combination of Asgharnejad in view of Erkoboni for at least the same reasons.

In addition, claim 3 is separately patentable over a combination of Asgharnejad in view of Erkoboni because claim 3 requires that the polar organic solvent in the granulating fluid must be isopropanol. Asgharnejad only discloses the use of ethanol. See, col. 3, lines 4-6 of Asgharnejad. Erkoboni only discloses the use of water as the granulating fluid and thus does not even disclose the use of a polar organic solvent, much less the use of isopropanol, in the granulating fluid. Accordingly for this additional reason, the rejection of claim 3 should be reversed.

D. Group III – Claim 9

Claim 9 depends indirectly from claim 1. Because claim 1 is not obvious over Asgharnejad in view of Erkoboni for the reasons given above, it follows by statute that claim 9 is also not obvious over a combination of Asgharnejad in view of Erkoboni for at least the same reasons.

In addition, claim 9 sets forth the additional limitation that the hydrocolloid is added once substantially all of the polar organic solvent has been removed by the controlled drying step. Neither Asgharnejad nor Erkoboni discloses addition of a hydrocolloid at this point in the drying step. Erkoboni only appears to disclose addition of the hydrocolloid during the granulation step, i.e. prior to the drying step. Thus, this element of claim 9 is not present in either Asgharnejad or Erkoboni and claim 9 is separately patentable for this additional reason.

Issue 2: Whether claims 14-16, and 18-26 are obvious over McTeigue.

A. The Rejection

Claims 14-16, and 18-26 have been rejected under 35 U.S.C. §103(a) as being unpatentable over McTeigue. More specifically, the Examiner took the position that,

> The McTeigue et al patent discloses microcrystalline cellulose particles having a particle size up to about 220 microns with a particle size standard deviation of from about 75 to about 200 microns (see column 2, line 54), which embraces the microcrystalline cellulose granules of the instant claims.... Although the McTeigue et al patent only discloses the microcrystalline cellulose thereof as having a mean particle size up to 220 microns, the particle size standard deviation of 200 microns that is disclosed in the McTeigue patent does suggests [sic] microcrystalline cellulose particles that have a particle size of at least 250 microns is [sic – are] present in the McTeigue et al patent.... Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant(s) invention to use the microcrystalline cellulose particles of the McTeigue et al patent that have a particle size of 250 microns.

See pages 3-4 of the Final Rejection.

The Examiner has also taken the position that the microcellulose described by McTeigue, although its mean particle size does not exceed 220 microns, has a "similar utility" and that "[i]t is within the skill of the artisan to adjust the size of the microcrystalline cellulose particles [to arrive at the mean particle size range of claim 14 of the present application] for optimum effectiveness." Advisory Action at page 2.

B. The Examiner Has Not Demonstrated a Case of *Prima Facie* Obviousness

1. Group IV – Claims 14-16, 18 and 20-26

Claim 14 is directed to porous microcrystalline cellulose granules having a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, and a mean particle size of from about 250 microns to about 1500 microns, made by the process of claim 1.

McTeigue clearly states that the microcrystalline cellulose has an average particle size of about 160 to about 220 microns.[3] Thus, the range of mean or average particle size disclosed by McTeigue of 160-220 microns, does not overlap with the claimed range of about 250 to about 1500 microns. The Examiner appears to have conceded this point when he stated, "Although the McTeigue et al patent only discloses the microcrystalline cellulose thereof as having a mean particle size of up to about 220 microns..." See page 3, lines 24-26 of the Final Rejection.

However, the Examiner took the position that, "...the particle size standard deviation of 200 microns that is disclosed in the McTeigue patent does suggests [sic] microcrystalline cellulose particles that have a particle size of at least 250 microns is [sic – are] present in the McTeigue et al patent." This statement is simply irrelevant to a determination of the obviousness of claim 14 since claim 14 does not require that the particle size of particular microcrystalline crystalline cellulose particles must be at least about 250 microns. Rather, claim 14 requires that the mean particle size of the microcrystalline cellulose must be at least about 250 microns. Thus, the fact that the McTeigue microcrystalline cellulose may contain some particles having an individual particle sizes in excess of 250 microns does not render claim 14 obvious because the

[3] "Mean particle size" and "average particle size" are known to the skilled person as being synonymous.

fact remains that McTeigue clearly discloses that the average or mean particle size of its microcrystalline cellulose should be from 160-220 microns.

The Examiner also took the position that,

> Applicants [sic] argument with regard to the differences in particle size [sic – mean particle size] of the microcrystalline cellulose of the instant claims at 250 microns and 220 microns in the McTeigue et al patent is not persuasive since the microcrystalline cellulose of the McTeigue et al patent set forth similar utility for the products, their use for preparation of tablets. It is within the skill of the artisan to adjust the size of the microcrystalline cellulose particles for optimum effectiveness.

See Advisory Action, page 2.

First, McTeigue does not set forth a similar utility for the microcrystalline cellulose as is claimed in the present application, i.e. for cushioning controlled release particles during the tabletting process to help preserve their controlled release characteristics. In fact, a close reading of McTeigue demonstrates that the microcrystalline cellulose of McTeigue is used for a totally different purpose than the microcrystalline cellulose of the present invention.

More specifically, McTeigue clearly teaches that,

> The present invention is directed to a particle which comprises a seed core comprised primarily of microcrystalline cellulose, ... to which a pharmaceutically active ingredient in solution is layered onto the microcrystalline cellulose by spray coating.

See col. 1, lines 40-45 of McTeigue. Thus, in the McTeigue pharmaceutical composition, the microcrystalline cellulose forms a seed core and the pharmaceutically active ingredient is spray coated onto the microcrystalline cellulose. In contrast, the utility of the granules of the present invention is in pharmaceutical compositions wherein the pharmaceutically active ingredient is included in controlled release particles and the controlled release particles and microcrystalline

cellulose granules are formed into a tablet by tabletting them together under high pressure. See e.g. page 3, line 21 to page 4, line 9 of the specification. As a result, there is no disclosure in McTeigue that the microcrystalline cellulose of McTeigue needs to have certain properties sufficient to provide cushioning of controlled release granules during a tabletting operation.

Secondly, the Examiner says that, "It is within the skill of the artisan to adjust the size of the microcrystalline cellulose particles [of McTeigue] for optimum effectiveness [in order to arrive at the mean particle size of claim 14 of the present application]." See the Advisory Action, page 2. There is a major flaw in the Examiner's reasoning. Specifically, if skilled person were to adjust the size of the microcrystalline cellulose particles of McTeigue for optimum effectiveness, the skilled person would follow the express teachings of McTeigue that the preferred source of microcrystalline cellulose has an average or mean particle size of 180 microns, and therefore would use an average or mean particle size of about 180 microns when optimizing the McTeigue composition. See e.g. col. 2, lines 40-41 and 48-50 of McTeigue. As a result, optimization of the mean or average particle size of the McTeigue microcrystalline cellulose leads a skilled person further away from the claimed invention, rather than to the claimed invention.

Therefore, the Examiner has not set forth a *prima facie* case of obviousness against claim 14 of the present application.

Claims 15-16, 18 and 20-26 depend, directly or indirectly, from claim 14. Because claim 14 is not obvious over McTeigue for the reasons given above, it follows by statute that claims 15-16, 18 and 20-26 are also not obvious over McTeigue for at least the same reasons.

Accordingly, Appellant respectfully requests that the rejection of claims 14-16, 18 and 20-26 under 35 U.S.C. § 103(a) be reversed.

2. Group V – Claim 19

Claim 19 depends indirectly, from claim 14. Because claim 14 is not obvious over McTeigue for the reasons given above, it follows by statute that claim 19 is also not obvious over McTeigue for at least the same reasons.

In addition, claim 19 is separately patentable over McTeigue since the mean particle size range of claim 19 is from about 400 microns to about 900 microns. There is no teaching, suggestion or motivation anywhere in McTeigue to employ a mean particle size in this range or anywhere close to this range, since the upper limit of the mean or average particle size disclosed in McTeigue is 220 microns, as discussed above. Moreover, the Examiner has completely failed to set out any case of obviousness against the subject matter of claim 19, much less a case of *prima facie* obviousness, since the Examiner has nowhere even alleged that it would be obvious to modify the teachings of McTeigue to arrive at microcrystalline cellulose having a mean or average particle size of at least about 400 microns.

Accordingly, for the foregoing reasons, the rejection of claim 19 under 35 U.S.C. §103(a) over McTeigue et al should be reversed.

Issue 3: Whether Claim 17 is obvious over McTeigue in view of Kumar.

A. The Rejection

Claim 17 has been rejected under 35 U.S.C. §103(a) as being unpatentable over McTeigue in view of Kumar. More specifically, the Examiner relies on the disclosure of McTeigue, as discussed above with respect to Issue 2. See page 4, lines 13-14 of the Final Rejection. The Kumar patent is cited by the Examiner to support the proposition that microcrystalline cellulose with a density range of 0.20 to 0.45 g/ml is well known in the art, based on col. 5, lines 46-48 of Kumar. See the Final Rejection at page 4, lines 16-19. From this, the Examiner concludes that,

> ...it would have been obvious to one having ordinary skill in the art to substitute the microcrystalline cellulose having a density of 0.4 g/cc of the McTeigue et al patent for the microcrystalline cellulose that comprises a density range of 0.20 to 0.45 g/ml of the Kumar patent, in view of the recognition in the art, as evidenced by the Kumar patent, that microcrystalline cellulose has inherent binding and superior tableting flow properties.

See page 4 of the Final Rejection.

B. Group VI – Claim 17

Claim 17 depends directly from claim 16. As discussed above, claim 16 is directed to porous microcrystalline cellulose granules having an irregular shape, a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, and a mean particle size of from about 250 microns to about 1500 microns.

As noted above, McTeigue neither teaches nor suggests microcrystalline cellulose having a mean particle size greater than 220 microns. See col. 1, lines 54-55 of McTeigue. Kumar

teaches that the microcrystalline cellulose should have a density of 0.2 g/ml to 0.45 g/ml and a particle size range of 150-200 microns. See col. 9, lines 21-22 of Kumar. Thus, the mean or average particle size of the microcrystalline cellulose of Kumar must be within the range of 150-200 microns since it is mathematically impossible for the average or mean particle size to fall outside of the overall particle size range due to the methodology used to calculate mean or average particle size, i.e. summing the sizes of all of the particles in the composition and dividing by the total number of particles in the composition. Accordingly, in the light most favorable to the Examiner, Kumar discloses microcrystalline cellulose having an average or mean particle size of 150-200 microns.[4]

The Examiner concludes that it would be obvious to substitute the microcrystalline cellulose of McTeigue for the microcrystalline cellulose of Kumar in order to arrive at the present invention. The applicant, however, cannot comprehend this argument since neither Kumar nor McTeigue teaches or suggests the microcrystalline cellulose of the present invention, i.e. having a mean particle size of at least about 250 microns. Thus, in the applicant's view, it matters not whether the microcrystalline cellulose of McTeigue or the microcrystalline cellulose of Kumar is employed, the skilled person simply cannot arrive at the present invention since neither Kumar nor McTeigue disclose microcrystalline cellulose having a mean particle size of at least about 250 microns.

Finally, the Examiner also took the position, with respect to claim 17, that,

[4] Note that for the microcrystalline cellulose of Kumar to have an average or mean particle size of 150 or 200 microns, all of the particles would have to be of the identical size of 150 or 200 microns, respectively, to meet the criteria of Kumar that the microcrystalline cellulose must have a particle size in the range of 150-200 microns.

> Applicants argue against the rejection of the claims over the McTeigue et al and Kumar patents on the grounds that the patents do not teach the granules, as claimed. However, this argument is not persuasive since there is no process step in the patents that involve [sic] spheronizing the microcrystalline cellulose. Also, see column 2, lines 54-57 and Fig. 1 of the McTeigue et al patent whereby an irregular shape [sic – irregularly shaped] surface of the microcrystalline cellulose is indicated, which embraces microcrystalline cellulose in granular form.

Final Rejection, paragraph bridging pages 4-5. Again, this position taken by the Examiner is not understood. The applicant had argued, for example, that Kumar discloses microcrystalline cellulose that has a particle size range of 150-220 [sic – 150-200] microns and that claim 17 required porous microcrystalline cellulose with a mean particle size of at least about 250 microns, and that there was no teaching or suggestion in Kumar to modify its teachings to arrive at the present invention. See August 26, 2002 response, page 4. The Examiner's response, thus, does not refute the basic argument made by the applicant.

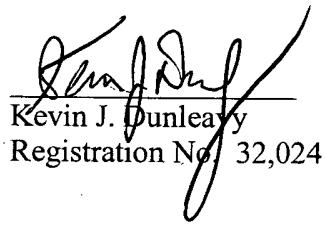
As stated above, a *prima facie* case of obviousness has not been made out when the prior art does not teach or suggest every limitation of the pending claim. By statute, claim 17 includes every limitation of claim 16. Thus, McTeigue and Kumar do not teach or suggest every limitation of claim 17 since the mean particle size limitation of claim 17 is not taught by either of these references as discussed above. Moreover, there is no teaching, suggestion or motivation in either McTeigue or Kumar to adjust the mean particle size of the microcrystalline cellulose granules in order to arrive at the mean particle size range of the claimed invention. Finally, there is no teaching or suggestion in either McTeigue or Kumar which would lead a skilled person to expect a beneficial result from increasing the mean particle size of the microcrystalline cellulose granules to at least about 250 microns. Therefore, it follows that the Examiner has not set forth a *prima*

facie case of obviousness since none of the three elements of a *prima facie* case is found in the references relied on by the Examiner. Accordingly, Appellant respectfully requests that the rejection of claim 17 as obvious over McTeigue and Kumar be reversed for at least these reasons.

IX. Conclusion

For the foregoing reasons, Appellant respectfully submits that each of the rejections should be reversed, and that the pending claims should be allowed. Such a decision is respectfully solicited.

Respectfully submitted,



Kevin J. Dunleavy
Registration No. 32,024

Date: April 25, 2003

KNOBLE & YOSHIDA, LLC
Eight Penn Center- Suite 1350
1628 John F. Kennedy Boulevard
Philadelphia, PA 19103
(215) 599-0600

APPENDIX: THE CLAIMS ON APPEAL

1. (Amended) A method for preparing porous microcrystalline cellulose granules comprising the following steps:

(a) granulating microcrystalline cellulose with a granulating fluid comprising water and a water-miscible, volatile, polar organic solvent to provide a granulated microcrystalline cellulose;

(b) drying the granulated microcrystalline cellulose at a controlled rate for a time sufficient to remove at least substantially all of the polar organic solvent from the granulated microcrystalline cellulose without removing at least a substantial portion of the water from the granulated microcrystalline cellulose, and without extruding or spheronizing the granulated microcrystalline cellulose from granulation step (a); and

(c) subsequent to step (b), removing at least a substantial portion of the water from the granulated microcrystalline cellulose.

2. The method of claim 1 wherein said polar organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, t-butyl alcohol and acetone.

3. The method of claim 2 wherein said polar organic solvent is isopropanol.

4. The method of claim 1 wherein the volume ratio of water to said polar organic solvent in said granulating fluid is from 85:15 to 15:85.

5. The method of claim 1 wherein the ratio of said granulating fluid to said microcrystalline cellulose in the granulating step is from 1:2 to 2:1.

6. The method of claim 1 wherein said granulated microcrystalline cellulose is initially dried at controlled temperature and pressure and once substantially all of the polar organic

solvent is removed, further drying is carried out at one or more of an elevated temperature, reduced pressure or both.

7. The method of claim 1 further comprising the step of adding to the granulated microcrystalline cellulose about 1 to about 30% by weight of a hydrocolloid, based on the weight of the granulated microcrystalline cellulose.

8. The method of claim 7 wherein the hydrocolloid is added to the granulated microcrystalline cellulose prior to the drying step which removes substantially all of the polar organic solvent component from the granulated microcrystalline cellulose.

9. The method of claim 7 wherein the hydrocolloid is added to the microcrystalline cellulose granules after substantially all of the polar organic solvent has been removed from the granulated microcrystalline cellulose.

10. The method of claim 7 wherein in the adding step the hydrocolloid is coated onto the surface of the microcrystalline cellulose granules.

11. The method of claim 7 wherein the hydrocolloid comprises one or more hydrocolloids selected from the group consisting of: methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, gelatin, water soluble cellulose acetate, polyvinyl pyrrolidone, starches, alginates, alginic acid, locust bean seed extract, guar seed extract, carrageenan, gum tragacanth, gum arabic and gum karoya.

12. The method of claim 11 wherein the hydrocolloid is selected from the group consisting of polyvinyl pyrrolidone, methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

13. The method of claim 11 wherein the hydrocolloid comprises polyvinyl pyrrolidone.

14. (Amended) Porous, granulated microcrystalline cellulose made by the process of claim 1 having a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, and a mean particle size of from about 250 microns to about 1500 microns.

15. (Amended) Porous, granulated microcrystalline cellulose made by the process of claim 7 having a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, and a mean particle size of from about 250 microns to about 1500 microns.

16. (Amended) Porous microcrystalline cellulose granules having an irregular shape, a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, and a mean particle size of from about 250 microns to about 1500 microns.

17. Microcrystalline cellulose granules as claimed in claim 16 having a loose bulk density of from about 0.25 to about 0.35 g/cc.

18. Microcrystalline cellulose granules as claimed in claim 16 having a mean particle size of from about 250 microns to about 1000 microns.

19. Microcrystalline cellulose granules as claimed in claim 16 having a mean particle size of from about 400 microns to about 900 microns.

20. Microcrystalline cellulose granules as claimed in claim 16 further comprising from about 1% to about 30% by weight, of a hydrocolloid, based on the weight of the granulated microcrystalline cellulose.

21. Microcrystalline cellulose granules as claimed in claim 20 wherein the hydrocolloid comprises one or more hydrocolloids selected from the group consisting of: methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, gelatin, water soluble cellulose acetate, polyvinyl pyrrolidone, starches, alginates, alginic acid, locust bean seed extract, guar seed extract, carrageenan, gum tragacanth, gum arabic and gum karoya.

22. Microcrystalline cellulose granules as claimed in claim 21 wherein the hydrocolloid is selected from the group consisting of polyvinyl pyrrolidone, methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

23. Microcrystalline cellulose granules as claimed in claim 21 wherein the hydrocolloid comprises polyvinyl pyrrolidone.

24. A tablet which comprises from about 5% to about 80% by weight of granulated microcrystalline cellulose as claimed in claim 16; from about 5% to about 80% by weight of one or more of controlled release particles and barrier coated materials which contain an active ingredient; and from 0% to about 20% by weight of other excipients, based on the weight of the tablet.

25. A tablet which comprises from about 5% to about 80% by weight of granulated microcrystalline cellulose as claimed in claim 20; from about 5% to about 80% by weight of one or more of controlled release particles and barrier coated materials which contain an active ingredient; and 0% to about 20% by weight of other excipients, based on the weight of the tablet.

26. A tablet which comprises from about 5% to about 80% by weight of granulated microcrystalline cellulose as claimed in claim 23; from about 5% to about 80% by weight

of one or more of controlled release particles and barrier coated materials which contain an active ingredient; and 0% to about 20% by weight of other excipients, based on the weight of the tablet.